RESEARCH REPORT

Leukemia

NATIONAL INSTITUTES OF HEALTH
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RESEARCH REPORT

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This *Research Report* begins with a description of how normal blood cells develop and what they do. It continues with information about the incidence, possible causes, symptoms, diagnosis, and treatment of leukemia—cancer that arises in blood-forming cells. The information presented in this *Research Report* was gathered from PDQ, the cancer information database developed by the National Cancer Institute (NCI); medical textbooks; recent articles in the scientific literature; and NCI researchers. A glossary of the *italicized* words in the text begins on page 47.

Knowledge about leukemia is increasing steadily. Up-to-date information is available by calling the National Cancer Institute-supported Cancer Information Service (CIS) toll free at 1-800-4-CANCER.

Leukemia is a complex disease, and there are several types of leukemia. This booklet was written to help the general public and health care workers better understand the leukemias and their treatment. Readers are encouraged to review pages 1 through 14. Those who are interested in a particular kind of leukemia may then want to read the information that pertains only to that type of leukemia.

How Blood Cells Are Made

To function properly, all parts of the body must be supplied with nutrients and oxygen; waste products—such as carbon dioxide (a *respiration* waste product) and urea (a *protein* waste product)—must be carried away. The blood carries out these functions by supplying vital nutrients and removing waste material.

Blood contains several types of cells suspended in a clear fluid called *plasma*. The process of blood cell formation and development is called *hematopoiesis*. This process begins in the *bone marrow*, the soft, spongelike material found in the cavities of bones, especially the breast bone, the ribs, the long bones, and parts of the hip. Most blood cells mature in the bone marrow, but some mature in the *thymus*, *spleen*, *lymph nodes*, and tonsils.

The various types of blood cells originate from one common ancestor known as a *stem cell*. Stem cells divide to form one of several types of very immature cells called *blast cells*. As shown in Figure 1, a normal blast cell goes through a series of changes (known as *differentiation*) to form one of three distinct types of blood cells: red cells (*erythrocytes*), white cells (*leukocytes*), and platelets (*thrombocytes*). The normal range of numbers for each type of blood cell is shown in Table 1.

Description and Function of Blood Cells

Red Blood Cells

Red blood cells (RBCs) contain *hemoglobin*, an iron-rich protein that carries oxygen from the lungs to all parts of the body and takes carbon dioxide from the cells back to the lungs. Cells need oxygen to obtain energy from the

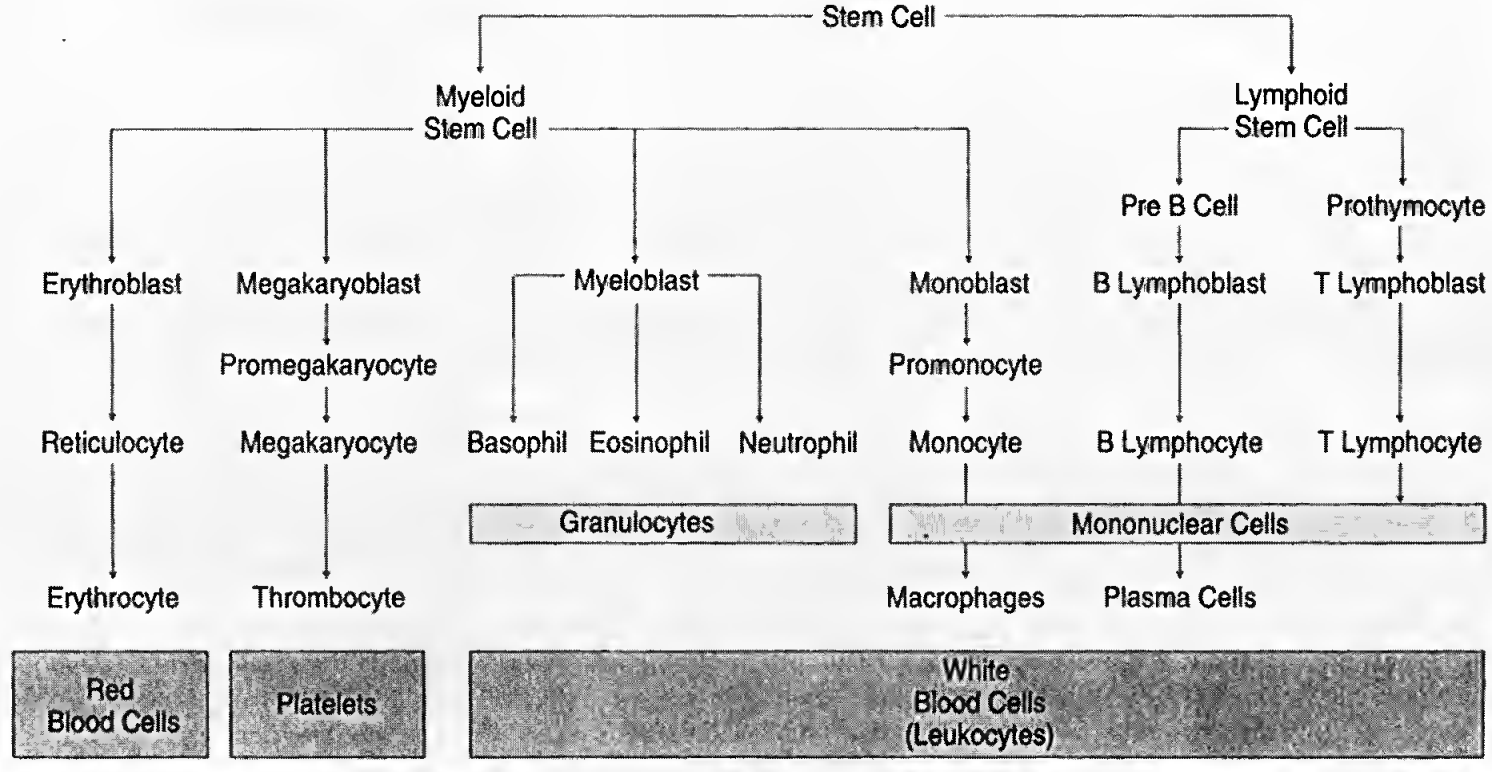
nutrients we eat. Having too few RBCs, a condition called *anemia*, makes it difficult for cells to get enough oxygen and can cause weakness, lack of energy, dizziness, headache, and irritability.

Table 1.
Normal Levels of Blood Cells

Type of Cell	Amount
White blood cells	5,000-10,000/mm^3 of blood
Neutrophils	50-60% of all white blood cells
Eosinophils	1-3%
Basophils	0-1%
Lymphocytes	25-35%
Monocytes	3-10%
Platelets	150,000-350,000/mm^3 of blood
Red blood cells	
In males	4.6-6.2 million/mm^3 of blood
In females	4.2-5.4 million/mm^3 of blood
Hemoglobin	
In males	14-18 grams/100 cm^3 of blood
In females	12-16 grams/100 cm^3 of blood

Source: Lamb, J.F., et al. *Essentials of Physiology*. Boston: Blackwell Scientific Publications, 1980, p. 424.

Figure 1. Normal Blood Cell Development



Platelets

Platelets prevent excessive bleeding by helping blood clot at the site of an injury. An abnormally low platelet count (*thrombocytopenia*) may result in excessive bleeding from wounds and in mucous membranes, skin, or other tissues.

White Blood Cells

White blood cells (WBCs) are the main components of the immune system, the body's defense mechanism that fights and destroys such foreign substances as bacteria and viruses. White blood cells are produced by stem cells in the bone marrow, but some mature outside the marrow in the lymph nodes, spleen, tonsils, and thymus. If an infection is present, the body produces extra WBCs. If the WBC count is abnormally low (*leukopenia*), a person's chance of developing an infection increases.

As shown in Figure 1, there are several major types of WBCs. Each has a specific function:

- *Granulocytes* fight infections caused by bacteria and have other roles as well. They are subdivided into *neutrophils*, *basophils*, and *eosinophils*.
  - —Neutrophils, also known as polymorphonuclear neutrophils (PMNs, or "polys"), are a primary defense against bacterial invasion. They perform this function partly through *phagocytosis*.
  - —Basophils play a special role in allergic reactions.
  - —Eosinophils are important in phagocytosis and allergic and inflammatory reactions.

- *Mononuclear* cells destroy invading *antigens*, particularly viruses. They mature mainly in the lymph nodes, spleen, and thymus, although some mature in the bone marrow. There are two main types of mononuclear cells: *lymphocytes* and *monocytes*.
  - —Lymphocytes regulate the *immune response*. The main types of lymphocytes are *B cells* and *T cells*. Some B cells produce specific *antibodies* (proteins) that help destroy foreign substances. It is believed that B cells mature in the bone marrow, but this has not been definitely established. T cells, which mature in the thymus, attack virus-infected cells, foreign tissue, and cancer cells; they produce substances that regulate the immune response.
  - —Monocytes (macrophages) play a key role in phagocytosis. They also interact with lymphocytes to regulate the immune response.

Types of Leukemia

Leukemia is cancer of the blood-forming cells. It occurs when immature or mature cells multiply in an uncontrolled manner in the bone marrow. It is classified as lymphocytic or myeloid, according to the type of cell that is multiplying abnormally, and either acute, signifying rapidly progressing disease with a predominance of highly immature (blastic) cells, or chronic, which denotes slowly progressing disease with greater numbers of more mature cells.

- Acute lymphocytic leukemia (ALL) begins in immature B or T lymphocytes (lymphoblasts).
- Acute myeloid leukemia (AML) begins in immature myeloid (nonlymphoid) cells (myeloblasts). Because nonlymphoid cells are affected, this type of leukemia is also referred to as acute nonlymphocytic leukemia (ANLL). There are a number of subtypes of AML.
- Chronic lymphocytic leukemia (CLL) is a disease of B lymphocytes.
- Chronic myeloid leukemia (CML) is also called chronic granulocytic leukemia. It begins in immature myeloid cells that would normally develop into granulocytes. CML belongs to a group of diseases called *myeloproliferative disorders.*
- Hairy cell leukemia (HCL), which arises from B lymphocytes, is so named because the abnormal cells have projections that resemble tiny hairs. It is a type of chronic leukemia.

Incidence and Survival Rates

In 1993, about 29,000 new cases (*incidence*) of leukemia—about 10 new cases per 100,000 Americans—were diagnosed, representing about 2.5 percent of all new cancer cases in that year. Of these, about 60 percent were acute leukemias. The incidence has declined by 8 to 9 percent over the past 17 years, except for black males, whose rate has remained fairly constant. Leukemias occur slightly more often in whites than in blacks. The male-to-female ratio is about 1.7 to 1; for CLL, the male-to-female ratio is nearly 2 to 1. As shown in Table 2, the incidence of the leukemias also varies by age.

Leukemia accounts for nearly one-third of all children's cancers, but it actually affects far more adults than children. In fact, fewer than 10 percent (2,500) of the 28,000 leukemia cases diagnosed in 1992 occurred in children. Ninety-five percent of childhood leukemia cases are acute; of this 95 percent, 75 percent are ALL and 20 percent, AML. ALL occurs predominantly in young children and in adults age 65 and older; AML occurs in infants, adolescents, and older people, but is unusual in young children (ages 2 to 10). Only 5 percent of childhood leukemias are chronic, and virtually all of these are CML. CLL almost never occurs in children and is rare before age 30; 60 years is the average age at diagnosis. CML is uncommon below the age of 20; half of all CML patients are over age 67.

Five-year *relative survival rates* for some types of leukemia have improved since the 1950s, with the largest improvements seen among children with acute lymphocytic leukemia. Before 1950, no effective chemotherapy was available for patients with acute leukemia. Effective single and multiple drug therapies were developed from the 1950s through the 1970s. In addition, *bone marrow transplantation* (BMT), introduced in the 1970s, has helped improve treatment for some patients with acute lymphocytic and nonlymphocytic leukemia. The most dramatic increase in survival rates for ALL has occurred in children between the ages of 2 and 10 years, whose relative survival rate increased from 52.5 percent from 1974 to 1976, to 72.3 percent from 1983 to 1988.

Table 2.
Leukemia Statistics

Type of Leukemia	*Median* Age* at Diagnosis (Years)	Annual Number of Cases per 100,000 People (1985-89)	Percentage of all Childhood Leukemia	Percentage of all Adult Leukemia**
Acute lymphocytic	11	1.5	75	6
Acute myeloid	67	2.3	20	54
Chronic lymphocytic	71	2.9	< 1***	25
Chronic myeloid	67	1.4	5	15
Hairy cell	53	< 1***	< 1***	2

*Half of all patients are above this age and half are below.
**Rounded upwards.
***Less than one.

Survival rates in the 1970s and 1980s for patients with chronic lymphocytic leukemia remained relatively unchanged at around 65 percent. The 5-year relative survival rate for patients diagnosed as having AML between 1983 and 1988 was only 10 percent.

Possible Causes of Leukemia

Although the causes of leukemia are not fully understood, certain factors are known to increase the risk of developing the disease. Among these are exposure to radiation, *genetic* and *congenital* factors, exposure to *mutagenic* chemicals, and infection with certain viruses.

Radiation

Light waves, microwaves, radio waves, radar, *x-rays*, and gamma rays are all forms of electromagnetic radiation. They differ in the *frequency* of the wave. The higher the frequency of the electromagnetic radiation, the more energy it contains and the greater its potential to cause biological changes. For example, microwaves have enough energy to vibrate water molecules; this is how they cook food. X-rays and gamma rays have so much energy that they can pass all the way through the body; they can damage cells by disrupting chemical bonds and creating *ions*. For this reason, they are referred to as forms of ionizing radiation.

Ionizing Radiation

Epidemiologic studies of patients with leukemia have conclusively linked the disease with exposure to high or repeated doses of ionizing radiation. When x-rays were first used, the incidence of leukemia among *radiologists* increased tenfold over that of the general population. In addition, a twentyfold to twenty-fivefold increase in the incidence of ALL, AML, and CML was observed in Japanese atomic bomb survivors 5 to 7 years after the explosions at Hiroshima and Nagasaki (no increase in CLL was observed). A study of people exposed to ionizing radiation (but at much lower doses than the Japanese survivors) from radioactive fallout from nuclear tests in

Nevada during the 1950s showed a slight increase over that of the general population in the incidence of acute leukemias in people under age 20. In 1986, many people were exposed to ionizing radiation following the nuclear power reactor accident at Chernobyl in the former Soviet Union. Scientists are monitoring these exposed individuals to see whether there is an increase in the incidence of leukemia.

Patients who received at least 2 grays (a measure of radiation) as treatment for ankylosing spondylitis, a painful condition of the spine, have an increased incidence of AML. Individuals exposed to diagnostic x-rays before birth have an increased risk of developing ALL by the age of 15 years. Some data suggest that 5 to 10 percent of patients who receive radiation and chemotherapy to treat Hodgkin's disease develop acute leukemia within 2 to 12 years after their first treatment. However, the small possibility of developing leukemia after therapy must be weighed against the known benefit of treatment for Hodgkin's disease.

Low-Frequency Electromagnetic Radiation

The electromagnetic radiation associated with the current supplied to households in the United States is of extremely low frequency (ELF) and, therefore, of very low energy. Although no one knows exactly how the electromagnetic fields (EMFs) associated with ELF radiation might cause cancer, some studies of groups of people exposed to EMFs have suggested a small increase in certain types of cancer in children and adults living near high-voltage transmission lines. There is some suggestive evidence of an association between childhood

cancer and residential electromagnetic field exposure, but limitations of these studies make it impossible to draw clear conclusions. Information on adult cancers does not suggest that residential electromagnetic field exposure is a risk factor, but, as with childhood cancer, data are too sparse to permit firm conclusions.

The Children's Cancer Group and NCI are collaborating on a large-scale investigation to determine whether exposure to ELF current contributes to the development of ALL in children under age 15. In this 5-year study, scientists will compare approximately 600 children having ALL with an equal number of similar children who do not have the disease. Researchers will then gather data on each group's exposure to ELF current to determine whether exposure increases the risk of ALL. Results of this study should be available in 1995.

Genetic and Congenital Factors

Genetic factors may increase a person's chance of developing acute leukemia. Studies of twins have demonstrated that if one identical twin develops acute leukemia before 6 years of age, there is a 20-percent chance that the other twin will develop the disease, frequently within months. Additionally, fraternal twins and siblings of patients with acute leukemia are at somewhat greater risk for the disease than is the general population.

People with certain chromosomal abnormalities have an increased risk of developing acute leukemia. Children with Down syndrome, a congenital condition in which

there is an extra *chromosome*, have 20 times the average incidence of acute leukemia. Other congenital disorders associated with chromosomal abnormalities and AML include Bloom syndrome, Fanconi's anemia, and von Recklinghausen's disease (neurofibromatosis).

Chromosomal abnormalities also have been found in the bone marrow cells of patients with acute leukemia who have no known congenital abnormalities. These leukemic chromosomal abnormalities disappear during *remission*.

In more than 90 percent of patients with CML, the leukemic cells have a unique chromosomal abnormality, the *Philadelphia chromosome* (Ph^1). The number of cells with this abnormality often may be reduced by therapy, but currently there is no way to completely rid the cells of the abnormal chromosome. The Ph^1 chromosome has also been observed in some patients with acute lymphoblastic leukemia who have no history of CML.

Environmental factors known to cause chromosomal abnormalities, such as ionizing radiation and chemical agents, also are associated with an increased incidence of acute leukemia, especially AML.

Chemicals and Drugs

Many chemicals have been associated with the development of leukemia. Workers exposed over long periods to benzene, an aromatic hydrocarbon present in gasoline and other products, are estimated to have a risk of developing AML 20 times greater than that of the general population. Drugs that can cause *aplastic anemia*, such as chloramphenicol and phenylbutazone, are associated with leukemia; so are certain other drugs

known as *alkylating agents*. Roughly 8 percent of patients treated with alkylating agents develop AML within 5 years after treatment begins. This finding does not suggest that patients treated with alkylating agents should stop or avoid their use, because, in general, their proven benefits far exceed their risks. However, these drugs should be used selectively in the treatment of cancer patients with low risk of relapse and individuals with noncancerous conditions.

Viruses

Scientists have known for years that *retroviruses* (also called RNA tumor viruses) can cause leukemia in mice, domestic cats, cattle, chickens, and gibbon apes. In 1980, NCI scientists identified the first human retrovirus, human T-lymphotrophic virus type I (HTLV-I), which they believe can be sexually transmitted or transmitted in blood or blood products. HTLV-I (sometimes referred to as human T-cell leukemia-lymphoma virus) is associated with two diseases: adult T-cell (lymphocytic) leukemia and a chronic degenerative neurologic disease termed HTLV-I-associated myelopathy with tropical spastic paraparesis (sometimes referred to as HAM/TSP). Adult T-cell leukemia was first reported in Japan. It has no known association with common leukemias, but it does resemble rare T-cell non-Hodgkin's lymphomas that begin in the skin (mycosis fungoides and Sézary syndrome). In Jamaica and the West Indies, HTLV-I is present in 40 to 60 percent of all patients with newly diagnosed adult non-Hodgkin's lymphoma. Some investigators have estimated that only 3 to 5 percent of people infected with HTLV-I early in life will develop adult T-cell leukemia. A recently developed test to detect the virus may provide more information about the *epidemiology* of HTLV-I.

Acute Leukemias

As noted earlier, leukemia is broadly classified as acute or chronic, and as lymphoid or myeloid. Acute leukemias seem to arise when the normal process of cell maturation (also called differentiation) is interrupted at a very early (blast) stage of a cell's life. The result is an accumulation of immature, nonfunctional, leukemic blast cells in the bone marrow and, to a lesser extent, in the blood.

Because blasts are immature blood cells, they usually make up less than 5 percent of the bone marrow and are not present at all in circulating blood. They normally mature or differentiate into various types of healthy, functioning blood cells. However, in the leukemia patient, blasts constitute more than 5 percent of cells in the marrow and may be found in the blood; they differ in appearance and function from normal blood cells. The distinction between acute lymphocytic leukemia and acute myeloid leukemia is that blast cells associated with ALL are those that would mature into lymphoid cells, whereas blasts that would mature into myeloid cells are associated with AML (see Figure 1).

Signs and Symptoms

Acute leukemias usually begin abruptly with intense symptoms and, if left untreated, are rapidly fatal. The early signs and symptoms of acute lymphocytic and acute myeloid leukemia are identical, and they also can be confused with those of common infectious illnesses. Fever and influenza-like symptoms frequently are the first signs. In children, the symptoms may be even more vague,

resembling the day-to-day changes in energy, appetite, and temperament seen in healthy children. For this reason, it is often difficult to make an early diagnosis of acute leukemia.

The signs and symptoms of acute leukemia are produced as blasts multiply and crowd the bone marrow, disrupting the normal production of other blood cells and spilling into the blood, where they circulate and invade vital organs. Many of the symptoms of acute leukemia are caused by the decrease in the number of healthy blood cells. The decrease in red blood cells produces such symptoms as fatigue, weakness, paleness, headache, and dizziness. With a decrease in platelets, a person may bruise or bleed easily. The decrease in functional white blood cells damages the body's ability to kill bacteria, fungi, and viruses, thus leading to frequent infections.

Other symptoms are caused by the leukemic cells themselves. The blasts invade organs, especially the lymph nodes, spleen, and liver, which become enlarged and painful, a condition known as organomegaly. Joint and bone pain are also common. In 25 percent of patients with acute leukemia, bone pain is one of the first symptoms reported; children with ALL may have joint pain accompanied by swelling and tenderness. Leukemic cells may also invade the *central nervous system* (CNS). Headache, blurred vision, confusion, altered thinking, or unexplained fever may occur when leukemia spreads to the CNS.

Because symptoms of acute leukemia are similar to those of a variety of nonmalignant conditions, it is important to check for other possible causes of symptoms, such as

infectious mononucleosis, aplastic anemia, systemic lupus erythematosus, or AIDS. It is also important to distinguish acute leukemia from other malignant conditions, such as lymphoma and chronic leukemia.

Diagnosis

Acute leukemia may be suspected if a blood test shows a low hemoglobin count, a low level of normal white blood cells, a low level of platelets, or the presence of leukemic blasts. However, as many as 10 percent of patients have normal total blood counts at the time of diagnosis (see Table 1). In such cases, the diagnosis can be confirmed only by *bone marrow biopsy*, in which a needle is used to withdraw (*aspirate*) a sample of bone marrow for examination under a microscope. As mentioned earlier, normal marrow contains fewer than 5 percent blasts, but the blast content of leukemic marrow ranges between 30 and 100 percent. Because the number of abnormal cells may vary from site to site within the marrow, it may be necessary to take several samples to assess the extent of disease.

Many laboratory tests are conducted with the bone marrow sample to make a diagnosis. The sample is examined by an experienced *oncologist*, *hematologist*, hematopathologist, or specially trained general pathologist. The cell's origin is identified so that the leukemia can be broadly classified as either lymphoid or myeloid. For example, the presence of rod-shaped granules, called Auer rods, in the leukemic cells identifies the disease as acute myeloid leukemia. Tests using stains and dyes help identify other types of cells, certain *cell surface markers*, and other cell characteristics.

Classification

Within each broad class of ALL or AML, systems have been devised to further classify the cells. Researchers identify cellular characteristics that are useful to plan treatment and to predict response to therapy. Using the French-American-British (FAB) classification system, ALL has been divided into subgroups L1 to L3; AML, into subgroups M0 to M7. A summary of each is presented in Tables 3 and 4. Some leukemias can have both lymphoid and myeloid features (biphenotypic) or, alternatively, some show no differentiation of either cell type (undifferentiated).

Table 3.
French-American-British Classification of Acute Lymphocytic Leukemia

Designation	Description
L1	The lymphoblasts tend to be small, with little *cytoplasm* and regularly shaped *nuclei;* they are more mature in appearance than other subtypes.
L2	The lymphoblasts appear more immature, varying in size and *nuclear* shape.
L3	The lymphoblasts tend to be large, with abundant cytoplasm and similarly shaped nuclei.

Table 4.
French-American-British Classification of Acute Myeloid Leukemia

Designation	Description
M0	Undifferentiated leukemia
M1	Acute myeloblastic leukemia with immature cells
M2	Acute myeloblastic leukemia with some mature cells
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5	Acute monocytic leukemia
M6	Erythroleukemia (immature red and white blood cells)
M7	Acute megakaryocytic leukemia [immature platelets (megakaryocytes)]

Leukemic cells are further classified by the presence of certain antigens on their surface. For example, the "common ALL antigen" (usually referred to as CALLA) is present on about one-half of lymphocytes in acute lymphocytic leukemia patients.

Treatment

Every leukemia patient should be treated by qualified hematologists or oncologists experienced in dealing with this disease. Patients should be treated in facilities with extensive supportive care capabilities, access to blood products, and a multidisciplinary team of physicians, nurses, and pharmacists.

The goal of treatment is to achieve *complete remission* (CR), the disappearance of all signs of disease (including all detectable leukemic cells) and the restoration of normal bone marrow function. Returning the level of blasts in the bone marrow to less than 5 percent and normalizing the blood cell counts are important objectives. However, CR does not always mean cure, because residual, undetected leukemic cells can later multiply and cause a *relapse.* Patients whose disease does not respond to treatment are said be *refractory* to treatment.

Great strides have been made in treating childhood ALL, which accounts for more than 75 percent of all cases of acute leukemia in children. It is now considered one of the most curable forms of cancer. Thirty years ago, a child with ALL, the major childhood leukemia, lived only about 3 months after diagnosis. Now, more than 95 percent of ALL patients can be expected to attain initial CR, and between 60 and 70 percent of children with ALL can be cured. Although advances in the treatment of childhood ALL have not been paralleled in adult ALL, 60 to 80 percent of adults with acute lymphocytic leukemia can be expected to attain CR, and 35 to 40 percent can be expected to survive 2 years. However, the cure rate of adult ALL remains low.

Steady progress has been made in the treatment of AML. Approximately 60 to 70 percent of adults with AML can be expected to achieve CR, as do 75 to 85 percent of children with this disease. New treatment approaches prolong survival for those who achieve a complete response: About 25 percent of adult AML patients who achieve a complete remission now survive 5 years or more.

The improved prognosis for many patients with acute leukemia has largely resulted from work done in *clinical trials* (treatment studies). In fact, research has shown that children treated in clinical trials do better than children who are not enrolled in clinical trials. For this reason, NCI encourages all patients with leukemia to consider taking part in clinical trials in which physicians are evaluating new forms of therapy. Information about clinical trials is found on page 45.

Types of Therapy

Chemotherapy, treatment with anticancer drugs, is the mainstay of treatment for leukemia. Chemotherapy is considered *systemic* treatment because the drugs travel through the bloodstream and can kill cells throughout the body. Combinations of two or more anticancer drugs may be given orally or *intravenously*. Some patients receive drugs *intrathecally* to destroy cancer cells in the central nervous system. Anticancer drugs are injected directly into the cerebrospinal fluid, which surrounds the brain and the spinal cord. High-dose chemotherapy is treatment with large doses of anticancer drugs in an effort to kill all the leukemic cells.

Radiation therapy, the use of high-energy rays to destroy cancer cells, also may be used to treat leukemia. Radiation therapy is a local treatment because only cells in the treated area are damaged.

- Involved field irradiation is the use of radiation therapy to kill cancer cells in an area of the body where they are known to be present. This area is called the involved field.
- Total-body irradiation may be used before bone marrow transplantation (see below) to kill leukemic cells. In this form of therapy, radiation is generally given in multiple doses over the course of several days to all areas of the body.

Bone marrow transplantation (BMT) is done to allow the administration of very high doses of chemotherapy and, in some cases, to provide the leukemia patient with disease-free bone marrow (see NCI's *Research Report: Bone Marrow Transplantation*). Marrow for transplantation can be obtained in three ways and is described by its source: another person (*allogeneic*), an identical twin (*syngeneic*), or the patient (*autologous*).

To prepare for BMT, patients receive large doses of drugs and/or radiation in an effort to destroy all leukemic cells. Dosages are so great that the patient's own bone marrow is destroyed, and the patient is totally dependent upon supportive care for control of bleeding and defense against infection.

In allogeneic transplantation, marrow is taken from a matched donor and infused into the patient's blood-stream. The donated cells travel from the blood to the

bone marrow where, in time, they usually become functioning marrow.

The success of allogeneic BMT depends partly upon how closely the donor's marrow genetically matches the recipient's marrow. Matching bone marrow involves comparing six characteristic proteins—markers called *human leukocyte antigens* (HLAs)—on the surface of white blood cells. The more closely the donor's HLAs match the patient's, the greater the chance of successful transplantation. Matching is also important to reduce the chance that the patient's body will reject the donor's marrow. The only perfect HLA match is between identical twins. The next best choice is between close relatives, such as siblings.

Matching also is important to decrease the risk of *graft-versus-host disease* (GVHD), a major complication of allogeneic BMT. In this disease, the donated marrow reacts against the patient's body. Although mild GVHD may be beneficial in some patients (because the donor's cells can destroy leukemic cells that remain in the body), severe GVHD is potentially fatal. In spite of improved matching techniques, GVHD is not uncommon. Currently, studies are in progress to find techniques that will help prevent GVHD.

Because the patient's own bone marrow is used, autologous bone marrow transplantation eliminates the risk of GVHD. During remission, marrow is removed, frozen, and stored for reinfusion should the patient relapse. To be sure any undetectable leukemic cells that may remain in the patient's marrow are destroyed, the marrow removed from the patient must be treated in a

process called *purging*. Researchers continue to look for more effective methods of purging and better ways to prepare patients for BMT. Therapy using BMT for leukemia patients with advanced, resistant disease has not been successful. Use of BMT earlier in the treatment plan has been more effective.

Biological therapy, another type of treatment, involves the use of substances known as *biological response modifiers* (BRMs). These substances are normally produced in small amounts as part of the body's natural response to cancer or other diseases. With modern laboratory techniques, scientists can manufacture large quantities of BRMs for use in cancer treatment. These BRMs may act directly to kill cancer cells or indirectly to change the way the patient's body reacts to a tumor; they also may enhance the body's ability to restore cells destroyed by chemotherapy. Several types of BRMs, such as those discussed below, are being evaluated in the treatment of leukemia:

- *Cytokines* are proteins formed in small amounts by all human cells to help regulate cell processes. *Interferons*, one type of cytokine, may augment a cancer patient's immune reaction against cancer cells. Cytokines also may act directly on cancer cells by inhibiting their growth or promoting their development into more normal cells.
- *Interleukins*, another type of cytokine, are produced by lymphocytes. Interleukins carry regulatory signals between blood-forming cells. Interleukin-2, one of the most-studied interleukins, stimulates the growth and activities of certain kinds of white blood cells.
- *Monoclonal antibodies*, another type of BRM, are tailor-made in the laboratory to recognize specific antigens on the surface of cancer cells. Monoclonal antibodies

are being used in autologous BMT to purge the marrow of cancer cells. Other uses for these antibodies in the treatment of leukemia are also under study.

- *Colony-stimulating factors* (CSFs) are proteins that stimulate bone marrow cells to divide and differentiate into platelets, red blood cells, and various specialized white blood cells. Studies are under way to determine whether CSFs that stimulate white blood cell production can help leukemia patients recover from the side effects of high-dose chemotherapy or increase the effectiveness of BMT. Interleukin (IL-3) and granulocyte-macrophage colony stimulating factor (GM-CSF) are being studied for their abilities to make leukemic cells more sensitive to antileukemic drugs.

Supportive Care

Supportive care is extremely important in the treatment of leukemia because both the treatment and the disease interfere with the patient's ability to produce red blood cells (which results in anemia, a low red blood cell count), white blood cells, and platelets. Patients with very low platelet and white blood cell counts are at great risk of life-threatening infection and bleeding; in fact, these are the two most common causes of death during the initial phases of treatment.

The purpose of supportive care is to prevent or reduce the effects of anemia, bleeding, and infection. The use of colony-stimulating factors is being studied to increase the number of white blood cells to help the body fight infection. Patients usually need periodic transfusions with red blood cells to control anemia. Transfusions of platelets reduce the rate of fatal hemorrhage, allowing treatment with anticancer drugs to continue even when the platelet

count has been very low. Sometimes, patients become resistant to platelets obtained from persons with a different platelet type. When this occurs, the patient's body recognizes the transfused platelets as foreign and rapidly destroys them; the patient is in danger of bleeding. Platelets are now grouped by HLA type (see page 23), and studies show that HLA-matched platelets often survive normally in patients who previously had developed resistance to nonmatched platelets. *Corticosteroids* are sometimes given prior to transfusion to improve the body's ability to use red blood cells and platelets.

During treatment, the health care team will perform a daily physical examination to look for signs of infection; this is an important component of leukemia therapy because it means that supportive measures can be taken as soon as the need arises. Because aggressive *antimicrobial therapy* is essential in the treatment of infectious complications, physicians are studying ways to administer antimicrobials so that infection can be controlled more effectively.

Childhood Acute Lymphocytic Leukemia

Treatment for children with ALL has become more sophisticated, and not all patients with this disease are treated on a uniform or "standard" treatment regimen. Because of the complex and intensive nature of ALL therapy, children should be considered for entry into a clinical trial in established pediatric cancer centers where state-of-the-art treatment is available. (Help in finding a center is available from many of the resources listed on pages 61 and 62; families are encouraged to contact the NCI-supported Cancer Information Service at 1-800-4-CANCER.)

The child's age, number of circulating leukemic cells, and microscopic features of the leukemia cells must be considered when therapy is being planned for ALL. Before beginning treatment, each child must have an initial evaluation that includes a physical examination, complex laboratory tests, and diagnostic x-rays. The laboratory tests include blood counts and chemistries and a urine test. Other procedures usually include a chest x-ray, a *bone marrow aspiration* (a needle is placed in a bone in the hip and marrow is drawn out), and a *spinal tap* (to determine whether leukemic cells are present in the spinal fluid).

Even though specific approaches to the treatment of children with ALL are variable, all regimens currently used usually fall into four main phases: remission induction, central nervous system *prophylaxis*, and consolidation therapy and maintenance treatment (postremission therapy).

Remission Induction—The goals of remission induction are to destroy all detectable leukemic cells and to reduce the number of blasts in the bone marrow to fewer than 5 percent. This phase of therapy, which usually lasts about 4 weeks, is an intensive stage of treatment, and the child must be closely monitored. In addition, social and emotional support are necessary to help both the child and the family cope with the stresses created by the illness and its treatment. The multidisciplinary health care team can help the family identify resources.

Many drug regimens are used in the treatment of ALL. A combination of vincristine, prednisone, and asparaginase produces remission in more than 90 percent of children with ALL. The addition of daunorubicin may somewhat

improve the rate and duration of remission. Researchers have found that a child's *prognosis* is heavily influenced by a number of factors, among them age, white blood cell count, and biologic features of the leukemic cell (for example, the extent to which a diseased cell resembles a normal one, as described in Table 3). Depending on these factors, doctors may begin treatment with a three- or four-drug regimen.

Studies are in progress to identify even more effective drug combinations for remission induction in childhood ALL. Researchers also are exploring whether the use of *granulocyte colony-stimulating factor* (G-CSF), a BRM that stimulates the growth of normal white blood cells, will allow the use of higher doses of chemotherapy and thus possibly produce longer-lasting remissions.

Central Nervous System Prophylaxis—It is uncommon for childhood ALL patients to have evidence of leukemia in the CNS at the time of diagnosis. However, scientists believe that undetected leukemic cells often are present in the CNS, where they are protected by the *blood-brain barrier* from the effects of remission induction chemotherapy. For this reason, the CNS is a frequent site of relapse after the initial treatment. During the remission-induction phase of treatment, children usually receive central nervous system prophylaxis to prevent CNS relapse. In CNS prophylaxis, children are given combinations of drugs (usually including methotrexate) that are injected intrathecally, with or without radiation to the brain.

CNS prophylaxis plays a vital role in the treatment of ALL; without it, patients run a significant risk of relapse. Yet CNS therapy itself has side effects. In one study,

children who received prophylactic CNS treatment with radiation and intrathecal therapy were compared with their healthy siblings. Investigators noted a higher rate of learning problems in the treated children. The effects were most pronounced in children who were treated before 5 or 6 years of age.

Intensive research is under way to find methods of CNS prophylaxis that provide effective protection from relapse without long-term side effects. Researchers are trying to identify the factors that determine the risk of CNS relapse. They already have found that patients with a good prognosis can be successfully treated without radiation to the brain. New information will help doctors tailor CNS therapy and use less intensive CNS treatment whenever possible.

Postremission Treatment (Consolidation and Maintenance)—Consolidation therapy involves short-term, intensive treatment; maintenance therapy is done over a longer period of time using lower doses of drugs. To maintain remission, some form of postremission treatment is essential. Many drug combinations and schedules are used to maintain remission, and therapy usually is given for 2 to 3 years.

Standard programs to sustain remission include weekly or biweekly methotrexate and daily 6-mercaptopurine, with intermittent doses of drugs such as vincristine and various corticosteroids. Eighty percent of patients in certain age groups (notably 2 to 10 years) who complete the full chemotherapy regimen without relapse remain disease free. Clinical studies to identify the most effective treatment are ongoing. Investigators are studying various

drug combinations, doses, and schedules to define the best postremission therapy for children with ALL.

Therapy at Relapse—The most common site of relapse is the bone marrow (*medullary* relapse). The incidence of relapse in the CNS has declined dramatically with the routine use of CNS prophylaxis. In boys with childhood ALL, the testes are another frequent site of relapse; when this happens, both testes are treated with radiation. In girls, relapse may occur in the ovaries. With either CNS or testicular or ovarian relapse, doctors assume that leukemic cells will be found throughout the body; they use a systemic treatment as well as local therapy.

Factors that influence a patient's ability to achieve a second remission include duration of first remission, previous therapy, and whether relapse has occurred in the bone marrow or elsewhere. Many children will achieve a second remission, although it is frequently short lived. However, in patients whose first relapse occurred at least 1 year after they completed initial treatment, therapy resulting in a second remission may be curative. Clinical studies to improve treatment for relapsed patients are ongoing. Among therapies being evaluated are new anticancer drugs and new combinations of drugs, BMT, and biological therapy with interferon and monoclonal antibodies.

Adult Acute Lymphocytic Leukemia

ALL is an uncommon type of leukemia in adults. It accounts for fewer than 20 percent of acute leukemia cases in adult patients.

Treatment of adult ALL is divided into three phases: remission induction, central nervous system prophylaxis,

and postremission treatment, called either remission continuation or remission maintenance. Unfortunately, adult ALL patients often relapse and require additional treatment. Each patient is physically evaluated before beginning chemotherapy. The procedures used to evaluate children, which are described beginning on page 27, are used for adults as well.

Remission Induction—The goals of remission induction for adults are the same as for children: to destroy all detectable leukemic white blood cells and to reduce the number of blasts in the bone marrow to fewer than 5 percent. This most intensive phase of therapy usually lasts from 4 to 7 weeks, during which patients require supportive care.

The combination of vincristine and prednisone produces remission (less frequently than in children) in 35 to 50 percent of adults with ALL. Recent studies show that the addition of either daunorubicin or doxorubicin increases the rate and duration of remission. Studies are in progress to identify even more effective drugs for remission induction and to evaluate the usefulness of adding G-CSF to therapy.

Central Nervous System Prophylaxis—Five to ten percent of adult ALL patients have evidence of leukemia in the CNS at the time of diagnosis. More than 40 percent develop CNS disease, but researchers have found that prophylactic CNS treatment often prevents it. The complications of CNS prophylaxis are less severe for adults than for children.

Currently, three treatment options are available: Intrathecal methotrexate combined with cranial irradiation; intrathecal methotrexate plus high-dose intravenous methotrexate without irradiation; and intrathecal chemotherapy alone.

Postremission Treatment—Some form of postremission treatment is essential to maintain remission. Maintenance programs for adults have been patterned after those used for children. Many drug combinations and schedules are used for remission continuation, and therapy usually is given for 1½ to 3 years. Bone marrow transplantation has been studied, but to date it has shown no clear advantage over chemotherapy alone. However, patients at high risk of relapse may be considered for BMT (either allogeneic or autologous) during the first remission or a subsequent one. As has been noted, however, the procedure itself has risks, and it is not appropriate for all patients.

Therapy at Relapse—Treatment for relapsed ALL depends on many factors, including the length of the previous remission and the site of the relapse. A number of clinical trials for adults with relapsed ALL are under way. These include high-dose combination chemotherapy (with or without irradiation) followed by BMT, use of new anticancer drugs and drug combinations, and biological therapy with monoclonal antibodies (see page 24).

Childhood Acute Myeloid Leukemia

Each year, about 600 children develop AML (also known as acute granulocytic leukemia or acute nonlymphocytic leukemia). Their prospects for successful treatment have improved considerably as the need for comprehensive supportive care has received greater attention. The treatment of AML is very different than for ALL. Therefore, laboratory diagnostic tests must be used to distinguish between the two. In certain cases, accurate diagnosis requires very sophisticated laboratory studies.

Remission Induction—Therapy for all subtypes of AML (see Table 4) is similar; chemotherapy is more intensive for AML than for treatment of ALL. Two drugs, daunorubicin

and cytarabine (ARA-C), form the mainstay of therapy. Additional drugs, such as thioguanine and etoposide, may be added. Remission induction frequently results in severe bone marrow suppression and requires extensive supportive care. Unlike adults, childhood AML patients may have evidence of leukemia in the CNS at the time of diagnosis, and CNS prophylaxis (see page 28) is usually included as part of remission induction.

Postremission Therapy–Additional chemotherapy or BMT is used to prolong initial remission in children with AML. The use of BMT for patients in first remission has been under evaluation since the late 1970s. Results on limited numbers of patients suggest that nearly 60 percent of children with matched donors who undergo allogeneic BMT during first remission have remissions longer than 3 years. Clinical trials are currently under way to determine whether intensive chemotherapy or autologous bone marrow transplantation can give results similar to those obtained with allogeneic BMT.

Therapy at Relapse—The single most active drug in children with AML who have relapsed appears to be ARA-C administered in high doses. Many other new agents are being evaluated in clinical trials, including mitoxantrone, diaziquone, idarubicin, and homoharringtonine. Amsacrine (M-AMSA), an investigational drug that has been under study for several years, has been shown to be useful against relapsed AML.

Many clinical trials are under way to find better treatments for children with AML. The roles of autologous and allogeneic BMT (see page 22) are being studied. In other trials, scientists are looking at new drugs and

biological response modifiers. Information about these trials is available from NCI's PDQ database, described on pages 45 and 46.

Adult Acute Myeloid Leukemia

Remission rates for adult AML have improved as a result of more effective chemotherapy and more intensive supportive care. As with childhood AML, therapy is similar for all subtypes of AML (see Table 4). Treatment consists of remission induction and postremission treatment.

As described for childhood ALL (see page 26), each AML patient's physical status is evaluated fully before treatment is begun. The doctor will order blood and other laboratory tests, blood and human leukocyte antigen typing, and tests to determine the blood's ability to coagulate (clot).

CNS prophylaxis is rarely indicated in adult AML (unlike childhood AML) because CNS relapse occurs in only a small percent of patients. However, patients with certain types of AML and those with high white blood cell counts are at greatest risk of CNS relapse; it is therefore important that these patients be evaluated by analysis of a sample of their spinal fluid. Those whose leukemia has spread to the CNS are treated with intrathecal chemotherapy.

Remission Induction—The combination of daunorubicin and ARA-C induces complete remission in approximately 65 percent of patients. Some physicians add 6-thioguanine, but there is little evidence that this improves the outcome of therapy. However, it has recently been suggested that the addition of etoposide to the induction

regimen lengthens remission. Trials are currently under way to evaluate the addition of other drugs, such as mitoxantrone and idarubicin, and higher doses of ARA-C. New anticancer drugs, such as tretinoin, also are under study for certain forms of AML.

During remission induction for AML, the two major potential complications are infection and bleeding. Patients require intensive supportive care, with frequent transfusions and broad-spectrum antimicrobial therapy.

Postremission Therapy—Although additional therapy is necessary in AML, no single postremission regimen currently is considered standard. Whether longer term therapy at lower doses (maintenance) or shorter term intensive therapy (consolidation) is preferable remains unclear. For this reason, patients are encouraged to consider participation in clinical trials at institutions where large numbers of AML patients have been treated.

At present, most adults with AML in first remission are treated with high-dose ARA-C alone, or followed by allogeneic or autologous bone marrow transplantation. All of these therapies have been demonstrated to prolong remission.

Therapy at Relapse—Patients with AML who have relapsed should be considered for treatment in clinical trials with new agents, such as amsacrine, mitoxantrone, diaziquone, high-dose ARA-C, homoharringtonine, idarubicin, and etoposide. At this time, however, the only potentially curative therapy for relapsed patients is allogeneic BMT. Studies to evaluate autologous bone marrow transplantation are in progress.

Chronic Leukemias

In chronic leukemia, too many mature white blood cells are produced and build up in the body. Early in the disease, the cells retain some ability to differentiate and perform essential functions. However, over long periods of time, the cells seem to lose these abilities; they become more abnormal and less functional. Chronic leukemias develop slowly, often with no symptoms, and may remain undetected for a long while.

As with acute leukemias, the chronic leukemias are classified according to the type of cell in which they begin; they are either chronic lymphocytic leukemia (CLL) or chronic myelocytic leukemia (CML). Together, these account for 40 percent of adult leukemias, and they are primarily diseases of middle and old age. CLL is twice as common in men as in women. The average age at diagnosis is about 60 years; the disease is rare before age 30, and it almost never occurs in children. CML is slightly more common in men than in women; although the average age at diagnosis is 45, CML does account for 5 percent of all childhood leukemias. The symptoms, diagnosis, and treatment of the chronic leukemias are described separately below. Because CLL and CML rarely affect children, only the adult forms of these diseases are discussed.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is a cancer in which lymphocytes multiply very slowly but in a poorly regulated manner, live much longer than normal, and are unable to perform their proper functions. More than 95 percent of CLL cases are of B-cell origin; the remainder are T-cell leukemias. In countries where HTLV-I infection

is *endemic*, such as Japan, Jamaica, and Trinidad and Tobago, between 3 and 5 percent of all people infected with this virus develop T-cell leukemia. B-cell CLL is very uncommon in Japan and other Asian countries, but T-cell leukemias appear to be endemic to certain areas of Japan. In the United States, there is some evidence of an increased incidence of T-cell leukemia in people with ancestral links to either Japan or parts of the Caribbean and South America.

Symptoms

About 25 percent of CLL patients have no symptoms, and the disease often is diagnosed as a result of a blood test for an unrelated complaint or while the doctor is investigating an enlarged lymph node or spleen (splenomegaly). People with CLL may have a general feeling of ill health, fatigue, lack of energy, fever, loss of appetite, or night sweats. Some patients have enlarged lymph nodes in the neck or groin; others show signs of splenomegaly, anemia, thrombocytopenia, or infection.

Diagnosis

Chronic lymphocytic leukemia may be confused with other related diseases, especially non-Hodgkin's lymphoma. CLL is suspected when blood tests reveal an increase in the number of lymphocytes in the blood to more than 15,000 per cubic millimeter (called *absolute lymphocytosis*). Frequently, CLL is diagnosed by identifying certain characteristics (called surface cell antigens or markers) on the lymphocyte's outside surface. The presence of these markers, along with the patient's age, is often sufficient to diagnose CLL, but diagnosis occasionally requires a bone marrow biopsy and more sophisticated chromosomal or other laboratory tests.

Once CLL has been diagnosed, more tests may be done to determine the extent of disease, a process called staging. Staging for CLL is different from staging for other leukemias in that it is used for treatment planning. At present, there is no one standard staging system for CLL. Based on one commonly used system (the Rai system), CLL is staged from 0 through IV, as follows:

Stage 0—More than 15,000 lymphocytes per cubic millimeter of blood (absolute lymphocytosis) is the only symptom.

Stage I—Absolute lymphocytosis and enlarged lymph nodes (*lymphadenopathy*) with no other symptoms.

Stage II—Absolute lymphocytosis, lymphadenopathy, and either an enlarged liver (hepatomegaly) or splenomegaly.

Stage III—Absolute lymphocytosis and anemia. Symptoms of lymphadenopathy, hepatomegaly, or splenomegaly may be present.

Stage IV—Absolute lymphocytosis and thrombocytopenia (fewer than 100,000 platelets per cubic millimeter), with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

In any stage, treatment planning is different for disease that has not responded to treatment (refractory disease) than for newly diagnosed and untreated disease.

Treatment

Treatment of CLL depends on the stage of disease and the patient's age and overall health. The course of CLL varies greatly from person to person. Some patients remain *asymptomatic* for many years; in others, the disease progresses more rapidly. Treatment can range from

periodic observation for patients without symptoms to treatment of complications such as infections to any of a variety of investigational therapies.

Because CLL cannot currently be cured with standard chemotherapy and often progresses slowly, it is generally treated conservatively. Anticancer drugs called alkylating agents are used for many patients; chlorambucil is the most active, but cyclophosphamide and others also are effective. These drugs are more effective when used in combination with such corticosteroids as prednisone. For patients with CLL localized to one area, irradiation of an involved lymph node or enlarged spleen (involved field radiation) can produce a response for months or years. In rare cases, surgery (called splenectomy) is required to remove an enlarged spleen. Transfusions of packed red blood cells and platelets are important in providing temporary relief for symptoms of anemia and thrombocytopenia.

The drug fludarabine phosphate (FAMP) can be used to treat B-cell CLL in some patients who have not been treated for their disease or who have not responded to therapy with an alkylating agent. Two other drugs have shown promise for patients with CLL who have not responded to standard treatment: 2-chlorodeoxyadenosine (2-CDA) and 2′-deoxycoformycin (pentostatin). Studies are in progress to more fully evaluate their effectiveness.

A number of studies are under way to define the role of biological therapy in treating CLL. Some involve interleukin-2 in combination with interferon; in others, monoclonal antibodies are being used (see page 24).

Because infections occur often in patients with CLL, immune globulin, a substance that contains antibodies, may be given to prevent infection. In addition, clinical studies are under way to determine whether the frequency of infection is reduced in CLL patients who are treated with intravenous immune globulin (IVIG). Clinical studies to improve treatment are ongoing. New anticancer drugs are being evaluated, and allogeneic and autologous BMT are being studied in young patients with CLL in an attempt to achieve a curative therapy.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML), classified as one of the myeloproliferative disorders, is a form of chronic leukemia that eventually progresses to a more acute form. In early CML, abnormal granulocytes multiply but usually retain their ability to differentiate and perform essential functions. In later stages of the disease, however, the leukemic cells lose the ability to mature and blast cells begin to build up in the bone marrow and blood. CML has three distinct phases: the chronic phase (the most common at diagnosis), the accelerated phase, and the blast phase (or crisis). In the chronic phase, there are few blast cells in the blood and bone marrow, and there may be no symptoms of leukemia; this phase may last from several months to several years. More blast cells and fewer normal cells are found in the bone marrow and blood in the accelerated phase; in the blast phase, more than 30 percent of the cells in the blood or bone marrow are blast cells. During blast phase, collections of blast cells may form tumors in the bones or lymph nodes.

Transition from the chronic phase to the accelerated and, later, the blast phase may occur gradually over a year or more, or it may occur abruptly; this new phase is referred to as "blast crisis." Blast crisis occurs an average of 3 to 5 years after diagnosis and is very similar to aggressive acute leukemia but is more difficult to treat.

Symptoms

Common early symptoms of CML are fatigue, tiring easily, weight loss, and a sense of fullness in the upper abdomen from an enlarged spleen, which is the most common finding at diagnosis (present in 90 percent of patients). The swollen spleen (splenomegaly) may fill most of the abdomen. Headaches, sweating, fever, and bone pain or tenderness also may occur. Patients with a low platelet count may have symptoms related to bleeding. However, many patients have no symptoms when they are diagnosed.

Diagnosis

To determine the cause of symptoms, doctors check the number of cells in the blood. If a person has CML, the doctor is likely to find an elevated white blood cell count (*leukocytosis*). In fact, the white blood cell count may be over 1 million per cubic millimeter. The majority of these cells will be mature or maturing myeloid cells such as granulocytes and basophils, but a few will be very immature (blast) cells. In 90 percent of patients with CML, the genetic material (chromosomes) in the majority of the cells in the bone marrow and blood cells will have an abnormality called the Philadelphia chromosome (Ph^1). This abnormality is an acquired genetic defect and is present only in blood cells and cannot be transmitted to offspring.

Treatment

Treatment other than BMT has rarely been successful in curing CML or preventing its progression from the chronic phase to a blast crisis. For this reason, patients with newly diagnosed disease are urged to consider participating in clinical trials exploring such new therapeutic approaches as BMT, use of biological response modifiers, and combination chemotherapy.

Patients whose blood counts are nearly normal may receive no treatment; however, they are followed carefully so that treatment may be given if the disease progresses. Symptoms may be relieved with oral doses of hydroxyurea or busulfan. Surgery to remove the spleen (splenectomy) may relieve physical discomfort or other problems resulting from a severely enlarged spleen. Patients in the chronic phase of CML respond well to treatment and may live normal lives even though the Ph^1 cells are not eliminated with standard chemotherapy. Recently, the biological response modifier interferon has been shown to control blood counts and enlarged spleen during the chronic phase in most patients and also can decrease the number of Ph^1 positive cells in the bone marrow. Researchers hope that treatment with interferon may result in prolonged remissions.

At present, the only known potentially curative treatment for chronic-phase CML is high-dose chemotherapy and total body irradiation followed by syngeneic or allogeneic BMT. Patients under 50 who have an identical twin or a sibling HLA-matched donor should be considered for BMT. In several studies, 50 to 70 percent of patients who had BMT in the chronic phase survived at least 2 to 3 years and some patients have now survived 10 to

15 years without relapse. Patients without a matched sibling donor may consider participating in clinical trials that are evaluating the effectiveness of transplantation from an unrelated matched or partially matched donor, autologous BMT with purging (see page 24), or studies with biological therapies.

When CML enters the accelerated phase, treatment may include increased doses of the drugs that the patient received in the chronic phase or the addition of other chemotherapeutic agents. In many cases, patients who were treated with busulfan alone during the chronic phase are treated with hydroxyurea. Patients who have severe anemia or thrombocytopenia are given supportive transfusions of red blood cells or platelets to relieve symptoms. Clinical trials of BMT are under way for patients in the accelerated phase.

The blast phase of CML is frequently very resistant to therapy, but various types of chemotherapy may be helpful in controlling symptoms. Radiation therapy also may be useful for pain control in CML patients with bone lesions. Patients with lymphoid blast crisis can respond to drug combinations used for ALL and generally survive longer than patients with myeloid blast crisis. However, remissions are generally very brief (3 to 6 months). Clinical trials include studies of BMT as well as combination chemotherapy, new chemotherapeutic agents, and biological response modifiers.

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a form of chronic leukemia arising in an unusual type of B lymphocyte that has hairlike projections. It accounts for approximately

2 percent of all leukemias and is five times more common in males than in females. The average age at diagnosis is 54 years.

Symptoms

Like other forms of chronic leukemia, hairy cell leukemia usually begins slowly. Symptoms are not dramatic and may include weakness caused by anemia, development of infections as a result of *neutropenia,* and pain or discomfort due to enlargement of the spleen.

Diagnosis

HCL is diagnosed when microscopic examination of a sample of lymphocytes reveals the characteristic hairy cell. Although hairy cells may not be found in the blood, they are always present in the bone marrow. However, in about one-half of all HCL patients, the marrow is *fibrous* (scarred) and impossible to aspirate, and diagnosis may require a bone marrow biopsy.

Treatment

HCL is easily controlled and may be cured in most patients. Many patients have prolonged survival with sequential therapies. About one-tenth of patients with HCL require no treatment. The decision to treat is based on blood counts, spleen enlargement, indications that the disease is progressive, or other complications.

Surgical removal of the spleen (splenectomy) may be recommended as the initial treatment for some patients. It is of greatest long-term benefit in patients with a very enlarged spleen and/or patients with only a few hairy cells in their bone marrow. About one-half of all patients treated with splenectomy need no additional treatment. Many HCL patients respond to interferon therapy but can relapse when interferon is stopped. Pentostatin also has

proven to be beneficial in HCL therapy. A new drug, 2-chlorodeoxyadenosine (2-CDA), can produce complete remissions in almost all patients. Very few of these patients have relapsed, and 2-CDA is now being given as primary therapy to most patients with HCL.

Other drugs also are being studied for HCL. Among the most promising is fludarabine. Bone marrow transplantation is being explored for young patients who are otherwise in good health but who have not responded well to other treatments. In addition, researchers are investigating whether the use of granulocyte colony-stimulating factors improves treatment success.

Clinical Trials and PDQ

To improve the outcome of treatment for patients with cancer, NCI supports clinical trials throughout the United States. Volunteers who take part in this research make an important contribution to medical science and may have the first chance to benefit from improved treatment methods. Physicians are encouraged to inform their patients about the option of participating in such trials. To help patients and physicians learn about current trials, NCI has developed PDQ, a computerized resource designed to give physicians quick and easy access to:

- Descriptions of current clinical trials, including information about the objectives of the study, medical eligibility requirements, details of the treatment program, and the names and addresses of physicians and facilities conducting the study;
- The latest treatment information for most types of cancer (also available by fax machine; the fax number is 301-402-5874); and

- Names and addresses of physicians and organizations involved in cancer care.

To access PDQ, physicians may use an office computer with a telephone hookup and a PDQ access code, or the services of a medical library with online searching capability. Cancer Information Service offices (1-800-4-CANCER) provide PDQ searches to callers and can tell physicians how to obtain regular access to the database. Patients may ask their physician to use PDQ or may call 1-800-4-CANCER to request a search themselves. Information specialists at this toll-free number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, treatment, and research.

Physicians wishing information about trials designed for children, teenagers, and young adults with leukemia may contact the attending physician at NCI's Pediatric Branch at 301-402-0696 (collect). Details of this service are explained in *The Pediatric Branch of the National Cancer Institute—A Guide for Referring Physicians*, NIH Publication No. 91-3226; this publication and other information may be obtained by writing to the Pediatric Branch at NCI, Building 10, Room 13N240, Bethesda, MD 20892.

Glossary

Absolute lymphocytosis: The presence of more than 15,000 lymphocytes in a cubic millimeter of blood.

Alkylating agents: Anticancer drugs that can damage the DNA of cells, leading to cell death.

Allogeneic bone marrow transplantation: A procedure in which a patient receives bone marrow from a compatible, though not genetically identical, donor.

Anemia: A below-normal number of red blood cells.

Antibodies: Proteins produced by certain white blood cells in response to the presence of foreign substances (antigens). Each antibody can bind to only one specific antigen. The purpose of this binding is to help destroy that antigen.

Antigen: Any substance that the body regards as foreign. When introduced into the body, an antigen causes the immune system to produce a corresponding antibody to fight it.

Antimicrobial therapy: Treatment to kill microorganisms (such as bacteria or fungi) or to suppress their growth.

Aplastic anemia: A form of anemia that occurs when the bone marrow fails to produce adequate numbers of blood cells.

Aspirate: To remove material from a body cavity by suction through a needle. Also refers to the material that is removed in this way.

Asymptomatic: Without symptoms.

Autologous bone marrow transplantation: A procedure in which bone marrow that had been removed from a patient is given back to that patient.

B cells: White blood cells, also known as B lymphocytes, that develop in the bone marrow and are capable of producing antibodies.

Basophil: A type of white blood cell. Basophils are one type of granulocyte.

Biological response modifier (BRM): A substance that boosts, directs, or restores the body's normal immune (defense) system. An example is interferon. BRMs are produced naturally in the body and can also be manufactured in the laboratory.

Blast cell: A very immature blood cell.

Blood-brain barrier: A network of blood vessels located around the central nervous system with very closely spaced cells that make it difficult for potentially toxic substances—including anticancer drugs—to penetrate the blood vessel walls and enter the brain and spinal cord.

Bone marrow: The soft, spongy tissue in the center of many bones; it produces white blood cells, red blood cells, and platelets.

Bone marrow aspiration: The removal of a sample of fluid and cells from the bone marrow for examination under a microscope. Aspiration is done with a needle. The results of the examination tell the doctor whether cancer cells are present.

Bone marrow biopsy: The removal of a sample of solid tissue from the bone marrow for examination under a microscope. The results of the examination tell the doctor whether cancer cells are present.

Bone marrow transplantation (BMT): A procedure in which doctors replace marrow destroyed by high doses of anticancer drugs and/or radiation.

Cell surface marker: An identifying substance on the surface of cells.

Central nervous system (CNS): The brain and the spinal cord.

Chromosome: A structure in the nucleus of a cell containing DNA, which transmits genetic information. Normally, 46 chromosomes appear as a long thread inside each human cell.

Clinical trial: Medical research conducted with volunteers. Each trial is designed to answer scientific questions and to find better ways to prevent or treat disease.

Clotting episodes: The inappropriate development of blood clots due to disease.

Colony-stimulating factors (CSFs): Proteins that stimulate the development of cells in the bone marrow.

Committed cells: Cells that have matured sufficiently so that microscopic examination can reveal what type of cell they will be when fully matured.

Complete remission (CR): The disappearance of all signs and symptoms of disease.

Congenital: Present at birth.

Corticosteroids: Complex chemical compounds produced in the outer layer of the adrenal gland, which is located near the kidney. They are important in regulating body chemistry. Corticosteroids can be manufactured in the laboratory and used as drugs.

Cytokines: Hormones or growth factors produced by cells that help regulate cell processes.

Cytoplasm: The fluid, liquid, or "watery" part of a cell; the cytoplasm surrounds the nucleus of the cell.

Differentiation: The process in which cells mature and become specialized.

DNA: Deoxyribonucleic acid; nucleic acid present in all living cells. DNA contains the genetic information of the cell.

Endemic: Constantly present in a population.

Eosinophil: A type of white blood cell. Eosinophils are one type of granulocyte.

Epidemiology: The study of the factors that determine how diseases are distributed in a community.

Erythrocytes: Red blood cells.

Fibrous: Containing fibers (threadlike noncellular structures). When bone marrow becomes fibrotic, it can be difficult to obtain a bone marrow sample.

Frequency: The number of times a wave pattern repeats.

Genetic: Inherited; having to do with information that is passed from parents to their children through DNA.

Graft: Tissue taken from one person (donor) and transferred to another person (recipient) or taken from one part of a person's body and transferred to another part of that same person's body.

Graft-versus-host disease: A condition that may develop after allogeneic bone marrow transplantation; the transplanted marrow (graft) attacks the patient's (host's) organs.

Granulocyte: A type of white blood cell. Neutrophils, eosinophils, and basophils are granulocytes.

Granulocyte colony-stimulating factor (G-CSF): A growth factor that promotes the production and development of granulocytes.

Group C status: A designation for investigational anticancer drugs that are effective against one or more forms of cancer but have not been approved for general marketing by the U.S. Food and Drug Administration. Doctors may obtain Group C drugs from the National Cancer Institute to treat patients who would benefit from their use.

Hematocrit: The percentage of blood that consists of red blood cells. Sometimes expressed as packed cell volume (PCV).

Hematologist: A doctor who specializes in studying and treating diseases of the blood.

Hematopoiesis: The formation and development of blood cells.

Hemoglobin: The protein found in red blood cells that carries oxygen. Hemoglobin gives blood its red color.

Host: In the case of organ or bone marrow transplantation, the recipient of the organ or marrow.

Human leukocyte antigens (HLAs): A series of proteins on the surface of cells that are important in transplantation and transfusion. When bone marrow transplantation is being considered, the HLAs on white blood cells (leukocytes) of the patient and the potential donor are compared. HLAs on platelets are matched when platelets are being transfused. A perfect HLA match occurs only between identical twins.

Immune response: The activity of the immune system against foreign substances (antigens).

Incidence: The number of new cases of a specific disease occurring during a given period.

Interferon: A protein produced by various cells in the body. Large quantities of different interferons may be produced in the laboratory. These proteins are used in the treatment of some forms of cancer. Interferon is a type of biological response modifier.

Interleukins: Proteins that carry regulatory signals between blood-forming cells. Large quantities of interleukins can be produced in the laboratory and used to treat some forms of cancer. Interleukins are biological response modifiers.

Intrathecal: Into the fluid around the brain and spinal cord—a way of injecting drugs.

Intravenous: Into a vein—a way of injecting drugs.

Ions: Atoms or groups of atoms that have an electrical charge.

Leukocytes: White blood cells.

Leukocytosis: An increase in the number of leukocytes in the blood.

Leukopenia: A below-normal number of white blood cells.

Lymph: The almost colorless fluid that bathes body tissues and carries cells that help fight infection.

Lymph nodes: Small, bean-shaped structures in the lymphatic system. The lymph nodes store special cells that can trap bacteria or cancer cells traveling through the body in lymph.

Lymphadenopathy: Disease of the lymph nodes.

Lymphocytes: A type of white blood cell.

Median age: In a list of ages arranged from youngest to oldest, the median age is in the center; half of the ages in the list are below the median and half are above it.

Medullary: In the central or inner portion; the medullary portion of bone is the bone marrow.

Metabolism: A general term for the physical and chemical processes and reactions to them taking place in the body. These processes are primarily concerned with the way nutrients are used in the body.

Monoclonal antibodies: Antibodies specific for a single target antigen. They can be produced in large quantities in the laboratory. Monoclonal antibodies are being studied in clinical trials to determine their effectiveness in cancer detection, diagnosis, and treatment.

Monocytes: One type of white blood cell.

Mononuclear cells: Monocytes and lymphocytes; white blood cells other than granulocytes.

Mutagenic: Causing a permanent change in genetic material (DNA).

Myelodysplastic syndromes: Conditions that result when blood cells fail to form or reproduce normally.

Myeloproliferative disorders: A group of diseases characterized by the abnormal excess growth of cells in the bone marrow.

Neutropenia: A below-normal number of neutrophils.

Neutrophil: A type of white blood cell (also known as a polymorphonuclear neutrophil). Neutrophils are a type of granulocyte.

NK (natural killer) cells: Large lymphocytes that attack certain cells on contact and probably help regulate the immune system.

Nuclear: Having to do with the nucleus of a cell. The nucleus is considered the control center of a cell.

Nuclei: Plural of nucleus.

Nucleus: The part of a cell that contains genetic information. The nucleus is considered the control center of the cell.

Oncogenic: Capable of causing cancer.

Oncologist: A doctor who specializes in studying and treating cancer.

Phagocytosis: The process by which phagocytes (literally, cell eaters) surround and destroy microorganisms or any foreign matter.

Philadelphia chromosome: An abnormality of chromosome 22 that is seen in bone marrow and blood cells of most patients with chronic myelogenous leukemia and some with acute lymphocytic leukemia. Also called Ph^1.

Plasma: The liquid portion of the blood.

Prognosis: The probable outcome or course of a disease; the chance of recovery.

Prophylaxis: An attempt to prevent disease.

Protein: A compound that is an essential part of plants and animals.

Purging: Removal of tumor cells from bone marrow before autologous transplantation.

Radiologist: A doctor who specializes in using radiation to diagnose or treat disease.

Refractory: Not responding favorably to treatment.

Relapse: The reappearance of signs and symptoms of disease after treatment.

Relative survival rate: A survival rate that takes normal life expectancy into account; the likelihood that a patient will not die of his or her disease by some specified time after diagnosis.

Remission: A period in which there is no evidence of disease on physical examination or examination of the bone marrow and blood.

Respiration: Breathing; the exchange of oxygen and carbon dioxide between the atmosphere and the body's cells.

Retrovirus: One of a large group of RNA viruses that are capable of copying and transferring genetic material.

RNA: Ribonucleic acid; nucleic acid present in all living cells. RNA controls protein synthesis by translating the genetic information within the cell.

Secondary leukemia: Leukemia (most often AML) that arises when bone marrow is damaged by chemotherapy given to treat certain types of cancer or other diseases.

Spinal tap: A procedure in which a needle is inserted into the space surrounding the spinal cord in order to withdraw cerebrospinal fluid. The cerebrospinal fluid is then analyzed in a laboratory for evidence of disease. Also called lumbar puncture.

Spleen: An organ in the abdomen that plays an important role in immune system activities; it is part of the lymphatic system.

Stem cells: The cells from which all blood cells develop. These cells may divide to form more stem cells or mature into a variety of blood cell types.

Syngeneic bone marrow transplantation: Grafting between two genetically identical individuals (identical twins).

Systemic: Affecting the body as a whole.

T cells: White blood cells that are important in the body's immune system. Also known as T lymphocytes, they mature in the thymus.

Thrombocytes: Platelets.

Thrombocytopenia: A below-normal number of platelets in the blood.

Thrombocytosis: A condition in which too many platelets (thrombocytes) are found in the blood.

Thymus: A small gland located in the top of the chest, behind the breastbone and between the lungs. The thymus plays a major part in the immune system.

Uric acid: A waste product created when the body digests and uses food and liquids.

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer.

Selected Readings

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Understanding the Immune System. National Institute of Allergy and Infectious Diseases and National Cancer Institute. NIH Publication No. 93-529.

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What Are Clinical Trials All About? Office of Cancer Communications, National Cancer Institute. NIH Publication No. 92-2706.

Young People With Cancer: A Handbook for Parents. Office of Cancer Communications, National Cancer Institute. NIH Publication No. 93-2378.

Chemotherapy and You: A Guide to Self-Help During Treatment. NIH Publication No. 92-1136.

Radiation Therapy and You: A Guide to Self-Help During Treatment. NIH Publication No. 94-2227.

Resources

American Cancer Society
1-800-ACS-2345

The American Cancer Society (ACS) is a national voluntary organization. It offers a wide range of services to patients and their families and carries out programs of research and education. It is financed through donations from individuals and private groups. Local chapters of ACS may be listed in the telephone directory; information is also available by dialing the toll-free telephone number listed above.

American Red Cross
17th and D Streets, NW
Washington, DC 20006
202-737-8300

The American Red Cross provides a range of services for emergency situations, collects and distributes blood and blood products, trains and provides volunteers who work with people in need of social service support, and does other relief work.

Leukemia Society of America
1-800-955-4572

The Leukemia Society of America is a voluntary organization that offers educational materials and information to leukemia and lymphoma patients and their families. It has many local chapters; their addresses may be listed in the telephone book; information is also available by dialing the toll-free telephone number listed above.

National Marrow Donor Program
Suite 400
3433 Broadway Street, NE
Minneapolis, MN 55413
1-800-654-1247

The National Marrow Donor Program (NMDP) is funded by a Federal contract with the American Red Cross, the American Association of Blood Banks, and the Council of Community Blood Centers. It was created to improve the efficiency and effectiveness of the donor search so that a larger number of unrelated bone marrow transplantations can be carried out. Businesses interested in setting up corporate recruitment programs may contact NMDP at 1-800-526-7809.

International Bone Marrow Transplant Registry
Medical College of Wisconsin
Post Office Box 26509
Milwaukee, WI 53226
414-257-8325

This research organization collects and analyzes data about allogeneic bone marrow transplantation. Most bone marrow transplantation treatment teams throughout the world participate in the registry. Staff are available to answer questions about the procedure. Donor matches are not made by this registry.

Additional Information

To obtain information on this subject and to order other NCI publications, call the toll-free Cancer Information Service (CIS) at:

1-800-4-CANCER

The CIS is a nationwide telephone service that answers questions from patients and their families, the public, and health professionals. Spanish-speaking staff members are available.

This *Research Report* has been approved by NCI scientists. Please direct questions or comments to the *Research Report* Editor, Office of Cancer Communications, National Cancer Institute, Bethesda, MD 20892.

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